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This Month in *AJP*

Cigarette Smoke Induces Proteolytic Microvesicles

Cigarette smoke damages the extracellular matrix in multiple locations, resulting in atherosclerotic plaque instability and emphysematous lung destruction. Li et al (**Am J Pathol 2013, 182:1552–1562**) inspected the underlying mechanisms by exposing human macrophages to tobacco smoke extract (TSE). They found that microvesicles (MVs) released from TSE-exposed macrophages carry active matrix metalloproteinase 14 (MMP14). TSE increased MMP14-positive MV production, which relied on JNK and p38 MAP kinase activation, MAPK-dependent MMP14 maturation, MMP14 accumulation into nascent plasma membrane blebs, and finally caspase- and MAPK-dependent apoptosis and apoptotic MV generation. These MVs may be a particularly potent pathway leading to extracellular matrix damage in tissues and organs of individuals exposed to tobacco smoke.

Kruppel-Like Factor 2 Modulates Inflammation

Kruppel-like factor 2 (KLF2) is a potent regulator of myeloid cell proinflammatory activation, with reduced KLF2 levels observed in patients with acute or chronic inflammatory disorders. Using $KLF2^{+/-}$ mice, Nayak et al (**Am J Pathol 2013, 182:1696–1704**) studied the biological response to inflammation. Partial KLF2 deficiency modulated the *in vivo* response to acute (sepsis) and subacute (skin) inflammatory challenge. The anti-inflammatory effects of KLF2 were linked to the inhibition of NF-κB transcriptional activity. This study provides biologically relevant insights into KLF2-mediated modulation of these inflammatory processes that could potentially be manipulated for therapeutic gain.

Anticancer Effect of ATP Citrate Lyase

ATP citrate lyase (ACLY) inhibition leads to growth suppression and apoptosis in some human cancer cells. Migita et al (**Am J Pathol 2013, 182:1800–1810**) found that selective depletion of ACLY was highly effective in the treatment of cancer cell lines displaying low levels of endogenous reactive oxygen species (ROS). ACLY inhibition enhanced mitochondrial ROS generation, which contributed to the anticancer effect of ACLY inhibition. ACLY inhibition-mediated ROS generation activated AMP-activated protein kinase (AMPK), which may sense intracellular ROS levels of cancer cells independent of the energy status. Basal AMPK activity in cancers might be a predictive biomarker for therapeutic response to ACLY inhibition.

miR-BART20-5p Inhibits T-bet in Nasal NK/T-Cell Lymphoma

Nasal NK/T-cell lymphoma (NNL) is an Epstein-Bar virus (EBV)-associated lymphoma derived from cytotoxic NK or T cells. Lin et al (**Am J Pathol 2013, 182:1865–1875**) studied the role of EBV-encoded miRNAs in invasive NNL. miR-BART20-5p was most strongly associated with invasion and lack of T-bet in NNL. The loss of T-bet expression in NNL was revealed to result from a block of T-bet translation by miR-BART20-5p. Additional data confirmed direct interactions between miRBART20-5p and T-bet mRNA and provided evidence that the mir-BART20-5p-p53 pathway is important in the pathogenesis of invasive NNLs. miR-BART20-5p is thus a marker for disease progression, and miR-BART20-5p antagomirs might be useful therapeutic agents in NNLs.

NF-κB Inhibition in Atherosclerosis

The inflammation regulator NF-κB controls the expression of many genes involved in atherogenesis. Mallavia et al (**Am J Pathol 2013, 182:1910–1921**) investigated the anti-inflammatory and atheroprotective effects of a cell-permeable peptide containing the NF-κB nuclear localization sequence (NLS). The NLS peptide blocked importin-mediated NF-κB nuclear import and lipopolysaccharide-induced pro-inflammatory gene expression, cell migration, and oxidative stress in vascular smooth muscle cells and macrophages. Systemic administration of NLS peptide had an atheroprotective effect in mice. Thus, targeting NF-κB nuclear translocation hampers inflammation and atherosclerosis development and identifies cell-permeable NLS peptide as a potential anti-atherosclerotic agent.

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